REMARKS

Status of the Application

Claims 23 and 27-49 are all the claims pending in the instant application. Applicant has amended claim 23 to better define the claimed invention. Support for the claim amendment can be found throughout the original specification and claims as originally filed, especially at least in paragraph [0056] of the specification. Accordingly, the amendments do not add new matter.

Claims 23 and 27-49 Define Allowable Subject Matter

A. Claims 23, 27-31, 36, 38-40 and 42-46 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Marler *et al., Plast. Reconstr. Surg.*, 105:2049-2058 (2000) ("Marler"), in view of Bent *et al.*, *Neurobiology and Urodynamics,* 20:157-165 (2001) ("Bent"), Kuo *et al., Biomaterials*, 22: 511-521 (2001) ("Kuo"), and Vanderhoff *et al.*, (WO 1996/39464) ("Vanderhoff").

B. Claims 32-35, 37, 41 and 47-49 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Marler, Bent, Kuo, Vanderhoff, Grandolfo *et al., Calcified Tissue International*, 52: 42-48 (1993), and Wong *et al., Alginates in Tissue Engineering*, 238: 77-86 (2003).

In making the rejection, the Examiner asserts that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention was made to use alginates, crosslinked with calcium and sodium and uncrosslinked, in the form of microsphere, for increasing the volume of tissue in a subject, as instantly claimed since the use of such is taught using analogous alginates (having different molecular weight range) for the same purpose." Pages 5-6, *Office Action of 12 May 2010.* Applicants respectfully disagree in that the cited references actually teach away from the presently claimed invention, particularly from injecting a composition comprising microparticles that are fully-crosslinked prior to the injection as set forth in dependent claim 23.

As pointed out in MPEP § 2145, "[i]t is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)."

As discussed in the Pre-Appeal Brief of 23 January 2010, Marler, Bent, and Vanderhoff teach away from the presently claimed invention. First, Marler (page 2053) shows that a pre-gelled alginate injection retains only about 30% of its volume 8 weeks post-injection and thus teaches away from pre-gelling of the alginate. Second, Bent also teaches away from the presently claimed invention as Bent's pre-gelled alginate degrades to the point so that "[t]he remaining cells then secrete a natural matrix, which maintains the volume of the original injection … ." Page 158, 2nd full para. Accordingly, one of ordinary skill in the art would be deterred from adopting Bent's alginate to increase tissue volume as claimed in the present application. Third, Vanderhoff also teaches away from the claimed methods, as Vanderhoff explicitly emphasizes that covalent cross-linking is strongly preferred and, in fact, explicitly discourages the reader from using ionic cross-linking. See Page 9, lines 30 – page 10, line 4. The Examiner also states that these problems with ionic cross-linking detailed in Vanderhoff apply only to calcium ions. *See* Page 9, *Office Action of 15 Oct. 2009*. Applicants respectfully disagree as Vanderhoff does not, in fact, limit its comments to the context of calcium cross-linking. Instead, Vanderhoff makes a general statement about ionic cross-linking and then states that these problems can be surmounted using covalent cross-linking. Thus, Vanderhoff teaches away from the ionic bonds used in the claimed methods, which require ionically cross-linked alginate.

Moreover, the newly cited reference of Kuo fails to cure the deficiencies of the other cited references and also teaches away from the presently claimed invention. In particular, Kuo teaches a slow cross-linking system so that the "system would allow hydrogels to be injected into the body at a specific site, or being molded into any complex geometry before gelation occurs" Right column, page 517. Kuo's hydrogel, due to the slow crosslinking system, essentially contains un-crosslinked (and, if at all, only some few partially crosslinked) alginate particles. Accordingly, Kuo teaches away from fully-crosslinking alginate before injection but

injects un-crosslinked alginate and carries out a crosslinking reaction, if at all, *in vivo* subsequent to injection.

Further, Applicants submit that Kuo has a completely different objective from the claimed invention, as Kuo is directed to the preparation of (a larger) alginate-implants and discusses the underlying problem of combining different calcium sources and gelling conditions to form gels at controlled gelation rates to meet the needs of different biomedical applications. *See* Page 512, left column, first paragraph. Additionally, Kuo only discloses *in situ* polymerisation of polymers having a molecular weight of 373 and 463 kDa (see page 515, right column) but not the use of a high weight polymer in fully crosslinked microparticles and their long term stability *in vivo* as the claimed invention achiveves. Thus, the underlying problem of Kuo, i.e. combining different calcium sources and gelling conditions to form gels at controlled gelation, is based on the assumption that product quality allegedly cannot be ensured when using dripping techniques, such as dripping sodium or potassium alginate solution into an aqueous solution of calcium ions typically made from calcium chloride ($CaCl_2$). According to Kuo, the fast gelation rate with $CaCl_2$ allegedly leads to varying crosslinking density and a polymer gradient within the gel bead. Kuo proposes the use of slow gelling $CaCO_3$-GDL (D-glucono-d-lactone) and $CaCO_3$-GDL-$CaCO_3$ systems as a solution to this problem that form structurally uniform gels as scaffolding materials for tissue engineering applications.

For the reasons set forth above, Applicants submit that the cited references teach away from combining the references to reach the presently claimed invention of injecting a composition comprising microparticles that are fully-crosslinked prior to injection as recited in claim 23. In addition, Applicants respectfully assert that the rest of the rejected claims are allowable over the cited references at least because of their dependency from independent claim 23 and the reasons set forth above.

Moreover, as MPEP § 716.02(a) states, "[e]vidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. 'Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness.' ... *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) …

[p]resence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)." Applicants submit that it was surprising and unexpected for the present inventors to find that fully crosslinked microparticles showed a superior and unexpected good long term stability in *in vivo* administrations. Even more surprisingly, the molecular weight of the fully crosslinked alginate microparticles turned out to be the most important relevant parameter for increasing long-term stability of these microparticles *in vivo*. This correlation between the molecular weight of the used alginate and the stability of fully crosslinked microparticles *in vivo* has never been reported or suggested before. Unexpectedly, increasing the molecular weight of the alginate in combination with ionical cross-linking also led to a significant increase in the long-term stability and biocompatibility of the fully crosslinked implants *in vivo*, an effect, which has not been reported or suggested by any of the above mentioned cited references. In other words, the highly pure alginate with a molecular weight of between about 100kDa and about 1200kDa, which has been ionically fully cross-linked prior to administration, exhibits significantly improved properties (in particular long-term stability and biocompatibility) and is particularly crucial for these properties *in vivo*, particularly when compared to the (low molecular weight) alginate material used in the methods disclosed in the cited art, even more particularly when compared to the (low molecular weight) covalently cross-linked alginate material used in Vanderhoff and the slow gelling techniques as shown by Kuo.

In the Examples of the present application, the inventors have implanted an alginate having a molecular weight of between about 100kDa and about 1200kDa. In this context, it is confirmed that all examples of the present invention have been carried out using alginates having a molecular weight of between about 100kDa and about 1200kDa. All these implants utilizing inventive fully crosslinked microparticles, showed a significantly improved long-term stability and which maintains its volume of up to 90% even after 6 months of implantation. Indeed, all implanted beads (100%,) were identified after 6 months, with their total weight corresponding to about 85 to 90% of the initial weight, and with the bead diameters corresponding to more than 95% of the initial values. These inventive fully crosslinked microparticles also showed a superior biocompatibility.

These unexpectedly superior properties were also confirmed in a 24 month long-term study with four fully crosslinked types of alginate microparticles (test items 1 to 4) prepared and administered according to the present invention. Each of the test items 1 to 4 used in the long term study (High M Ca-Beads, High M Ba-Beads, High G Ba-Beads and 1% High M alginate solution, wherein these High M alginates exhibiting a mannuron/guluron acid ratio of the alginate of 60%/40%, and High G alginates exhibiting a mannuron/guluron acid ratio of the alginate of 40%/60%) comprised the highly pure alginate with a molecular weight of between about 100kDa and about 1200kDa. All of these test items showed a very good biocompatibility and a particularly good long-term stability, wherein the stability and biocompatibility were determined after 1 week, 3 months, 6 months, 12 months and 18 months. All four test items showed no signs of degradation during the study. Additionally, the results confirmed the above findings that the implanted high-molecular weight maintains its volume of up to 90% even after 6 months of implantation. Even further, the implanted inventive fully crosslinked microparticles were identified in a significant amount after a period of 12 months and even a period of 18 months (see intermediate study report, chapter 4.4, 4.5 and 5). As an additional benefit, at no time any erythema or edema at the implantation sites were observed, which confirms the excellent biocompatibility of the high molecular alginates used according to the inventive method. In other words, the inventive method clearly avoids the strong inflammatory reactions as observed in Vanderhoff. In the study, histological sections of implantation sites were performed, which were evaluated semi-quantitatively with respect to local tolerance parameters, including inflammatory cells (polymorphonuclear cells, lymphocytes, plasma cells, macrophages, giant cells), necrosis, fibroplasia, fibrosis and fatty infiltration in accordance with the standard ISO 10933-6:1994. In addition, tissue degeneration, fibrin, encapsulation, neovascularization and possible degradation of the material were assessed. Advantageously, no Giant cells and no polymorphonuclear cells could be observed at the implantation site after eighteen or even twenty-four months of implantation. The implantation of beads furthermore induced in no case any necrosis even after eighteen or even twenty-four months of implantation.

As a further illustration, the following photographs are provided show that exemplary macroscopic photographs taken during taxidermy after 12 months of implantation (see

Appendix, Figure 1) as well as H&E stainings of implantation sites with test item 1 (High M Beads Ca^{++}) after 12 months of subcutaneous implantation in the rat (see Appendix, Figure 2) and H&E stainings of implantation sites with test item 2 (High M Beads Ba**; B), after 18 months of subcutaneous implantation in the rat (see Appendix, Figure 3). They confirm again an excellent biocompatibility and long-term stability of the inventive fully crosslinked microparticles used according to the present invention.

As already outlined above, an excellent biocompatibility and long-term stability of the inventive fully crosslinked microparticles used according to the present invention could be demonstrated in the long-term study.

None of the cited references teaches or suggests the use of such inventive fully-crosslinked microparticles being fully crosslinked and having the specified molecular weight for the inventive purpose, particularly for increasing tissue volume in a subject. The present invention thus provides a more stable alginate composition that can be formed at controlled gelation rates to meet the needs of different biomedical applications and is also safer *in vivo*.

For the foregoing reasons, Applicants respectfully submit that the claims are not rendered obvious by the cited references and request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Appendix

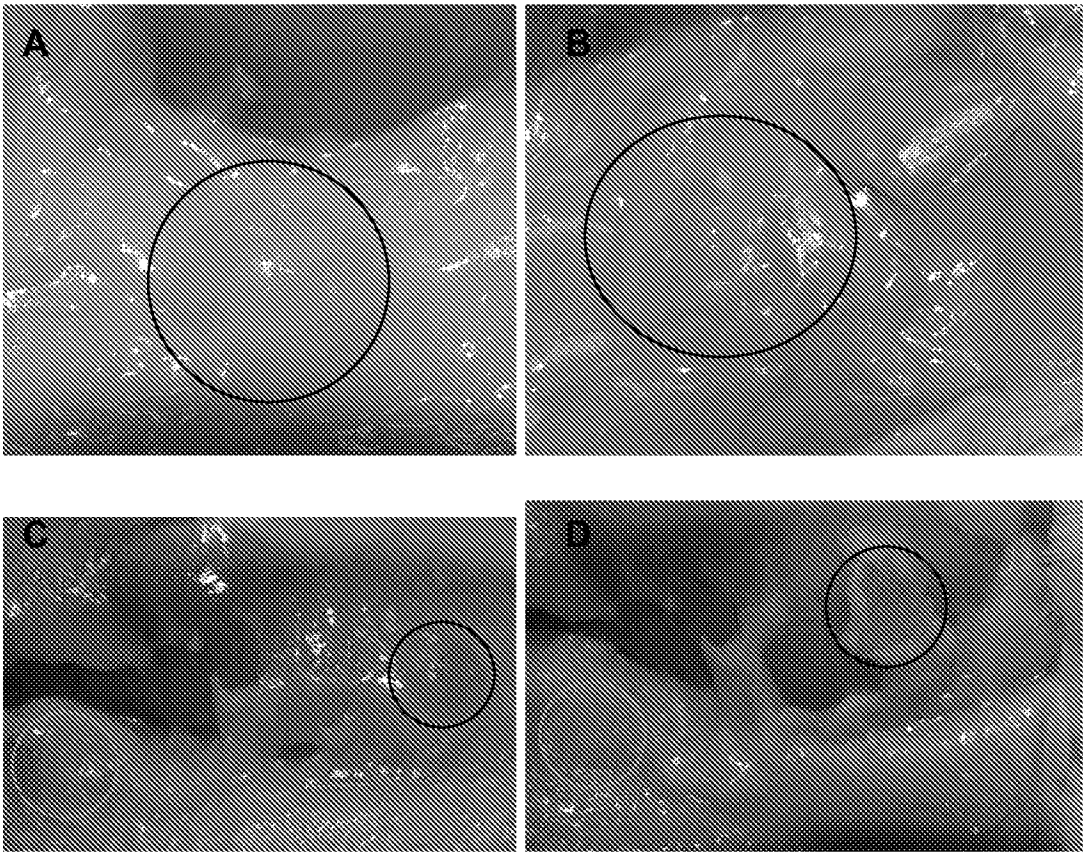

Figure 1: Macroscopic photographs during taxidermy after 12 months of implantation. A: test item 1 (High M Ca-Beads) on the inner layer of the skin; B: test item 4 (alginate) on the inner layer of the skin under fatty tissue; C: test item 3 (High G Ba-Beads) on the muscle (black circle) and test item 2 (High M Ba-Beads) on the inner layer of the skin (blue circle); D: test item 3 (High G Ba-Beads) on the muscle (black circle) after opening of the surrounding tissue layer and test item 2 (High M Ba-Beads) on the inner layer of the skin (blue circle) after opening of the surrounding tissue layer.

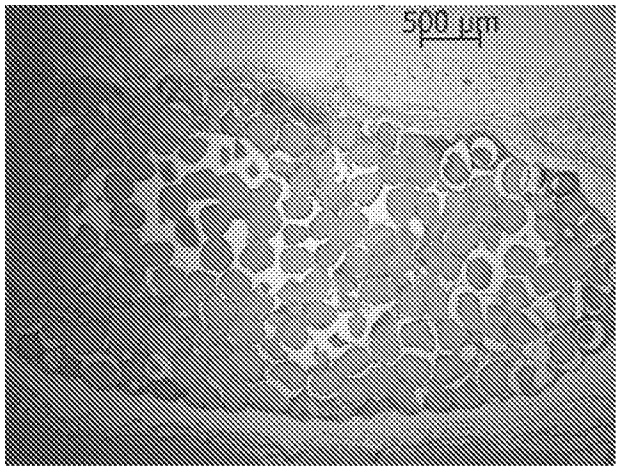

Figure 2: H&E stainings of implantation sites with test item 1 (High M Beads Ca^{++}) after 12 months of subcutaneous implantation in the rat.

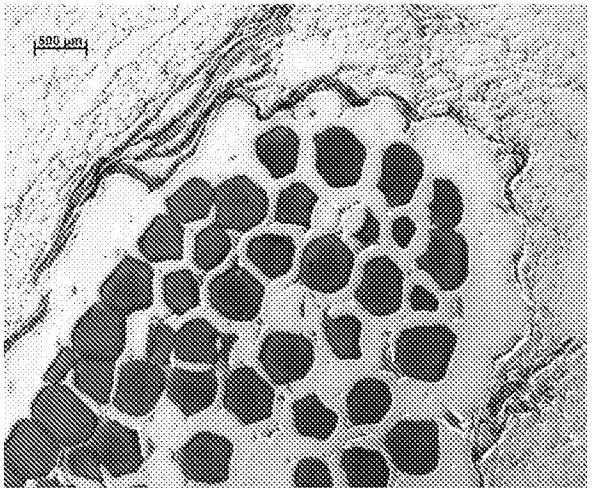

Figure 3: H&E stainings of implantation sites with test item 2 (High M Beads Ba**; B), after 18 months of subcutaneous implantation in the rat.